The Earliest Roots of Adult Disease

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The Ohio State University
Objectives

• Describe the concept of fetal origins of adult diseases
• Discuss how “epigenetics” plays a role in shaping development during and after pregnancy
• Understand the differences between breast and bottle fed infants in terms of future health risk
Health Risk
Parenthood begins at conception.
Epigenetics = the Role of the Environment

What if our genes are turned on or off by our experiences?
The Dutch Famine

Hunger Winter in Holland, 1944-45

Daily rations: 400-1000 kcal

Pregnancy outcomes tied to famine

Clement Smith MD:

Babies born to malnourished mothers
  - Lower birth weight by 200 grams
  - Brain damage & poor mental performance
  - Higher obesity rates among males
Follow Up of Dutch Famine Cases

- 2414 cohort born during the famine
- Now aged 50-58 years
- Famine’s effect: early, mid-, late-gestation
- Consequences in diverse systems:
  - Glucose-insulin axis
  - Cardiovascular risk factors
  - Renal function
  - Airway disease
  - Breast cancer

Roseboom, 2006
Evolution of an Idea

Neel (1962):

“the thrifty genotype”

- During evolution, when food was scarce, efficient fat storage enhanced survival
- During abundance, such genes cause obesity, insulin resistance, diabetes and heart disease
Evolution of an Idea

- Hales and Barker (1992): “the thrifty phenotype”
  - With poor nutrition, the fetus adapts to survive
  - With abundance later in life, such adaptations result in diseases and obesity

*Our adult health begins as a fetus*
Pregnancy “Programs”
Adult Diseases

- Obesity
- High blood pressure
- High cholesterol
- Heart disease
- Stroke
- Diabetes
- Mental health disorders
Nutrition is only one Stress that Forces the Fetus To Adapt
Not Just *Nutritional* Stress

- Energy or protein
- Placenta
- Blood flow
- Corticosteroids
- Smoking
- Alcohol
- Toxins
- Oxygen
- Blood sugar
Epigenetics

Diet Quality
Pre-pregnancy/ Pregnancy/ Postnatal
Too little/ Imbalance/ Too Much

Tissues Remodel
Function Changes
Cells Dysfunction
Metabolism Changes

DEVELOPMENT SHIFTS

Structure and Function Changes
Body composition
Heart & Blood vessels
Appetite and energy control
Hypertension: *Kidney*

- Very low protein within a “critical window”

- **Adaptations**
  - Decrease total number of cells
  - Increasing single-nephron work load
  - Development of scarring
  - Nephrons die off
  - Sodium builds up in blood
  - High blood pressure

*Adaptations as a fetus*

*Becomes “maladaptive” as an adult*

*Brenner BM, et al*
“Epigenetics” means...

What happens to mom
Happens to baby
Maternal Stress
Van den Bergh BRH, et al.

High stress can cause behavioral changes in the child

- Stress = “stress hormones”
  - Physical demands
  - High fatigue score
  - Sleeplessness
  - Mental stress
  - Trauma, injury, illness

Mental and behavioral health problems in the child
Even Before the Pregnancy Test

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 5-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>The embryo implants</td>
<td>Brain vesicles</td>
</tr>
<tr>
<td>Week 3-4</td>
<td>Spinal, cranial nerves</td>
</tr>
<tr>
<td>Notocord, neural folds</td>
<td>Heart valves</td>
</tr>
<tr>
<td>Head, tail, soma</td>
<td>Coronary vessels</td>
</tr>
<tr>
<td>Heart tubes</td>
<td>Metanephric kidney</td>
</tr>
<tr>
<td>Optic vessels</td>
<td>Gut lumen</td>
</tr>
<tr>
<td>Fore-, hind-brain</td>
<td></td>
</tr>
<tr>
<td>limbs</td>
<td></td>
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</table>

...much has already developed
Women in Child-bearing Years

- Intake high:
  - saturated fat and sodium
- Deficiency common:
  - iron, vitamin D
- Intake low:
  - fiber, vitamin E, calcium, magnesium and potassium
- Intake moderately low:
  - vitamins A, C, B-6 and Folate
Excess Gestational Weight Gain

- Pre-pregnancy factors account for $\frac{3}{4}$ --
  - Age
  - Race/ethnicity
  - Education
  - Parity
  - Height
  - Pre-conception BMI
  - Diabetes
  - Hypertension
**High or Low Maternal Weight**

- Fetal growth and anomalies
- Macrosomia (obese), IUGR (underweight)
- Gestational hypertension, preeclampsia
- Gestational diabetes
- Preterm birth (underweight), spontaneous
- Preterm births (obese), medical
Weight Gain during Pregnancy

- Individualized by pre-pregnancy BMI
- Lowers risk for mother & baby
- Institute of Medicine, 1990

<table>
<thead>
<tr>
<th>BMI</th>
<th>Weight Gain (lbs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 19.8</td>
<td>28-40</td>
</tr>
<tr>
<td>19.8-26</td>
<td>25-35</td>
</tr>
<tr>
<td>26-29</td>
<td>15-25</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>35-45</td>
</tr>
<tr>
<td>Teens, Blacks</td>
<td>Higher end of ranges</td>
</tr>
</tbody>
</table>
Emphasize Diet Quality

NOT DIETS
2010 Dietary Guidelines

Meals and snacks from 5 food groups
- Fruits
- Vegetables
- Whole grains
- Low-fat milk and dairy
- Lean meats, quality protein

Control excess weight

Balance intake with daily activity

Nutrition from every calorie: “nutrient rich foods”
USDA Eating Pattern = Health

- Heart Disease
- Stroke
- Diabetes
- Obesity
- Hypertension
- Metabolic syndrome
- Osteoporosis
- Cancers

Dietary Guidelines for Americans 2010
The First Weeks *Add* Risks
What if there is a critical window for first feeding?
• Calories very low weeks 1-3 (lactation)
  – Free access to diet after
  – Slowed weight gain \textit{for life}

• Calories low in weeks 9-12
  – Slowed weight gain \textit{only briefly}

\textbf{Early life stress can cause permanent changes}
Experimental Evidence

- **Preterm infants** (926) randomized at birth to receive standard formula, donor breast milk or enriched pre-term formula
- 216 infants examined at age 13-16 years
- **Enriched formula**
  - $\uparrow$ Blood pressure
  - $\uparrow$ Cholesterol
  - $\uparrow$ Obesity
  - $\uparrow$ Insulin Resistance

Lucas and Singhal, 2003, 2004
The Critical Window

Singhal & Lucas (2004):
- Rapid weight gain programs the heart and metabolism for life
- Critical window: the first 2 weeks
Early Rapid Weight Gain Results in Increased Long-term Issues

- Weight gain during week 1 associated with adult obesity\(^1\)
- Rapid weight gain during the first 4 months of life is associated with obesity in childhood and young adulthood\(^2\)
- More rapid increases in weight-for-length in the first 6 months are associated with sharply increased risk of obesity at age 3\(^3\)

## Early Rapid Weight Gain Increases the Risk for Obesity

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Stettler, 2002</td>
<td>Pattern of rapid weight gain during first 4 months of life associated with being overweight at age 7(^1)</td>
</tr>
<tr>
<td>Dubois, 2006</td>
<td>Double the odds of being overweight at age 4.5 years if in the highest quintiles of weight gain between birth and 5 months(^2)</td>
</tr>
<tr>
<td>Taveras, 2009</td>
<td>Rapid increases in weight-for-length in the first 6 months of life associated with increased risk of obesity at age 3, predicted higher BMI, adiposity, and elevated systolic blood pressure at age 3(^3,4)</td>
</tr>
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BMI= body mass index.
### Early Rapid Weight Gain & Obesity

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<tr>
<td><strong>Chomtho, 2008</strong></td>
<td>Weight gain during early infancy is associated with increased fat mass and central fat distribution at 11 years&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Dennison, 2006</strong></td>
<td>Rapid weight gain from 0 to 6 months in WIC program predicts obesity at age 4&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Wells, 2011</strong></td>
<td>In obese individuals, ages 5-22, postnatal weight gain had the most dominant impact on adiposity and fat distribution&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

WIC= Women, Infants and Children.

Early Rapid Weight Gain May Impact Health Risk

CVD = cardiovascular disease.
Breastfeeding and Obesity

A Small but Significant Effect on Obesity
Breastfed / Formula Fed

- BF versus FF: *early growth differs*
- BF infants experience a greater *neonatal weight loss* and take longer to *regain birth weight* than FF infants

Crossland et al. 2009, Macdonald et al. 2003
Breast-fed: 6.4%
Formula-fed: 3.7%

Weight Loss at 2 Weeks

% Birth weight Lost
First Days of Life

• Composition and volume
  – Breast Day 1 & 2: 21 mL, 100 mL
  – Formula Day 1 & 2: 170 mL, 265 mL

• Maternal supply limits volume

• Does formula need lower calories to compensate for a higher volume of intake?
Infants Adjust Calories After 4-6 weeks

(kcal/kg/day)

Foman, 1974
The Changing Energy Content of Breast Milk

<table>
<thead>
<tr>
<th>Stage</th>
<th>kcal/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colostrum (Day 1-5)</td>
<td>536</td>
</tr>
<tr>
<td>Transition (6-14 d)</td>
<td>577</td>
</tr>
<tr>
<td>Mature (&gt; 14 d)</td>
<td>652</td>
</tr>
<tr>
<td>Infant Formula (Day 1)</td>
<td>676</td>
</tr>
</tbody>
</table>
Infant Formula > Mature Breast Milk

<table>
<thead>
<tr>
<th>Study</th>
<th>Calories/Liter</th>
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<tbody>
<tr>
<td>Infant Formula</td>
<td>676 kcal/L</td>
</tr>
<tr>
<td>Wojcik et al. 2009</td>
<td>650 kcal/L</td>
</tr>
<tr>
<td>Reilly et al. 2005</td>
<td>639 kcal/L</td>
</tr>
<tr>
<td>Hosoi et al. 2005</td>
<td>642 kcal/L</td>
</tr>
<tr>
<td>Mitoulas et al. 2005</td>
<td>633 kcal/L</td>
</tr>
<tr>
<td>Lucas et al. 1987</td>
<td>616 - 642 kcal/L</td>
</tr>
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</table>
The New WHO Standard vs the CDC 2000 curve

Mean weight-for-age Z-scores of healthy breast-fed infants

de Onis M, et al.
Parents are overfeeding
Can We Protect \textit{Non}-Breast Fed Infants Too?

- Breast fed in-hospital 74%
- Exclusively breast fed at 3 mos 31%
- Exclusively breast fed at 6 mos 11%
- Mix breast/bottle 4 months 36%
- Mix breast/bottle 6 months 43%
- Any breast feeding at 12 mos 23%

CDC, 2007
Teach Parents to Listen to Their Babies
Risk of Disease is Layered

- Preconception
- Genetics
- Pregnancy weight gain
- Maternal diet
- Stresses
- Breast vs bottle
- Early rapid weight gain
- Later excess weight gain
- Quality of dietary choices
So

• Adult diseases have fetal origins
• Pre- and post-natal stresses are epigenetic
• Epigenetic adaptations during development may become “maladaptive” later
• A “critical window” exists for early feedings of term, SGA and preterm infants
• **Now we walk a line** between the dangers of under- and over-nutrition for optimal health